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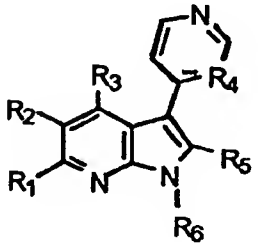
(57) Abstract

This invention relates to a series of pyrrolopyridines of Formula (I), pharmaceutical compositions containing them and intermediates used in their manufacture. The compounds of the invention inhibit the production of a number of inflammatory cytokines, are useful in the treatment of diseases associated with overproduction of inflammatory cytokines.



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SUBSTITUTED PYRROLOPYRIDINES USEFUL IN THE TREATMENT OF INFLAMMATORY DISEASES

This invention relates to a series of substituted pyrrolopyridines, pharmaceutical compositions containing them and intermediates used in their manufacture. The compounds of the invention inhibit the production of a number of inflammatory cytokines, particularly, TNF-α and IL-1β. Compounds of this invention are useful in the treatment of diseases associated with overproduction of inflammatory cytokines, such as rheumatoid arthritis, inflammatory bowel disease, septic shock osteoporosis and osteoarthritis.

BACKGROUND OF THE INVENTION

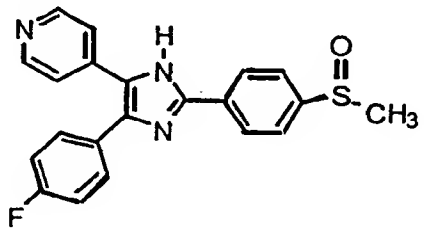
The inflammatory cytokines, IL-1β and TNF-α play an important role in a number of inflammatory diseases such as rheumatoid arthritis. C. Dinarello et al,. Inflammatory cytokines: Interleukin-1 and Tumor Necrosis Factor as Effector Molecules in Autoimmune Diseases *Curr. Opin. Immunol.* **1991**, *3*, 941-48. Arthritis is an inflammatory disease which affects millions of people and can strike at any joint of the human body. Its symptoms range from mild pain and inflammation in affected joints, to severe and debilitating pain and inflammation. Although the disease is associated mainly with aging adults, it is not restricted to adults. The most common arthritis therapy involves the use of nonsteroidal antiinflammatory drugs (NSAID) to alleviate the symptoms. However, despite their widespread use, many individuals cannot tolerate the doses necessary to treat the disease over a prolonged period of time. In addition, NSAIDs merely treat the symptoms of disease without affecting the underlying cause. Other drugs, such as methotrexate, gold salts, D-pencillamine, and prednisone are often used when patients fail to respond to NSAIDS. These drugs also have significant toxicities and their mechanism of action remain unknown.

Receptor antagonists to IL-1β and monoclonal antibodies to TNF-α have been shown to reduce symptoms of rheumatoid arthritis in small-scale human clinical trials. In addition to protein based therapies, there are small

molecule agents which inhibit the production of these cytokines and have demonstrated activity in animal arthritis models. J.C. Boehm et al., 1-Substituted 4-Aryl-5-pyridinylimidazoles: A New Class of Cytokine Suppressive Drugs With Low 5-Lipoxygenase and Cyclooxygenase Inhibitory Potency, *J. Med. Chem.*, **1996**, *39*, 3929-37. Of these small molecule agents, SB 203580 has proved effective in reducing the production of TNF-α and IL-1 in LPS stimulated human monocyte cell lines with IC_{50} values of 50 to 100 nM. J. Adams et al., Imidazole Derivatives And Their Use as Cytokine Inhibitor, International Patent application WO 93/14081, July 23, 1993. In addition to this in vitro test, SB 203580 inhibits the production of the inflammatory cytokines in rats and mice at IC_{50} values of 15 to 25 mg/kg. A.M. Badger, et al, Pharmacological Profile of SB 203580, A Selective Inhibitor of Cytokine Suppressive Binding Protein/p38 Kinase, in Animal Models of Arthritis, Bone Resorption, Endotoxin Shock and Immune Function, *The Journal of Pharmacology and Experimental Therapeutics*, **1996**, *279*, 1453-61. Although human data is currently unavailable for SB 203580, monoclonal antibodies to TNF-α have proved efficacious in the treatment of rheumatoid arthritis. M.J. Elliot et al., Treatment of Rheumatoid Arthritis with Chimeric Monoclonal Antibodies to Tumor Necrosis Factor α, *Arthritis Rheum.* 1993 *36*, 1681-90. Due to SB 203580's oral activity and potency in animal models, researchers have suggested that a compound with this profile has potential as a viable treatment for rheumatoid arthritis. A.M. Badger, et al. Pharmacological Profile of SB 203580, A Selective Inhibitor of Cytokine Suppressive Binding Protein/p38 Kinase, in Animal Models of Arthritis, Bone Resorption, Endotoxin Shock and Immune Function, *The Journal of Pharmacology and Experimental Therapeutics*, **1996**, *279*, 1453-61.

SB 203580 and other small molecule agents reduce the production of inflammatory cytokines by inhibiting the activity of a serine/threonin kinase p38 (note other researchers refer to this enzyme as CSBP), at an IC_{50} of 200 nM. D. Griswold et al., Pharmacology of Cytokine Suppressive Anti-inflammatory Drug Binding Protein (CSPB), A Novel Stress-Induced Kinase, *Pharmacology Communications*, **1996**, *7*, 323-29. Although the precise role of this kinase is

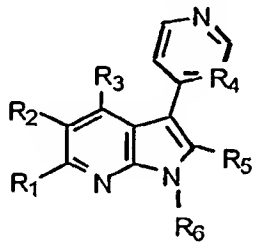
unknown, it has been implicated in both the production of TNF-α and the signaling responses associated with the TNF-α receptor.



SB 203580

SUMMARY OF THE INVENTION

The invention relates to compounds of the Formula I



I

wherein:

R_1 is amino, C_{1-5}alkylamino, diC_{1-5}alkylamino, hydroxy, C_{1-5}alkoxy, C_{1-5}alkylcarbonylamino, substituted phenylcarbonylamino where the phenyl substitutents are selected from the group consisting of halogen, hydrogen, C_{1-5}alkly, and C_{1-5}alkoxy, arylC_{1-3}alkylamino or $R_7R_8NCH=N$-

where R_7 and R_8 are independently selected from the group consisting of hydrogen and C_{1-5}alkyl;

R_2 is hydrogen, halogen, phenylC_{1-5}alkyl or substituted phenylalkyl where the phenyl substituents are selected from the group consisting of halogen, hydrogen. C_{1-5}alkoxy and C_{1-5}alkyl;

R_3 is hydrogen, hydroxy, C_{1-5}alkoxy, substituted phenyloxy, (where the phenyl substituents are selected from the group consisting of

halogen, hydrogen. C_{1-5}alkoxy and C_{1-5}alkyl), substituted phenylC_{1-5}alkyloxy (where the phenyl substituents are selected from the group consisting of halogen, hydrogen. C_{1-5}alkoxy and C_{1-5}alkyl);

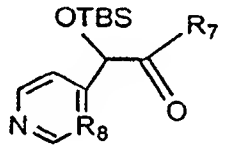
R_4 is -N- or -C-;

R_5 is phenyl or substituted phenyl where the substituents are selected from one to three members of the group consisting of halogen, C_{1-5}alkyl and C_{1-5}alkoxy;

R_6 is hydrogen, C_{1-5}alkyl or diC_{1-5}alkylamino;

and pharmaceutically acceptable salts thereof.

In addition, this invention contemplates a method of producing compounds of Formula II.



II

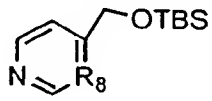
where

R_8 is -N- or -C- and

R_7 is phenyl or substituted phenyl where the substituents are selected form one to three members of the group consisting of halogen, C_{1-5}alkyl and C_{1-5}alkoxy,

These methods comprise

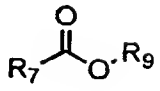
contacting a compound of Formula III



III

where R_8 is -N- or -C-,

with a compound of Formula IV



IV

where

R_7 is phenyl or substituted phenyl where the substituents are selected form one to three members of the group consisting of halogen, C_{1-5}alkyl and C_{1-5}alkoxy,

and

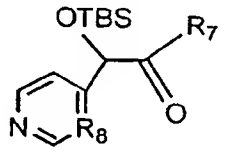
R_9 is C_{1-5}alkyl, phenylC_{1-5}alkyl, or phenyl,

in the presence of suitable base and a suitable solvent at about room temperature to about reflux until the formation of an enolate of a compound of Formula II; and

protonating said enolate with a mild acid to give a compound of Formula II.

Still further the invention contemplates a method of producing compounds of Formula I which comprises

contacting a compound of Formula II



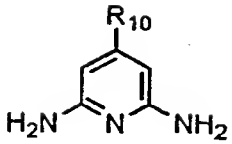
II

where

R_8 is -N- or -C- and

R_7 is phenyl or substituted phenyl where the substituents are selected form one to three members of the group consisting of halogen, C_{1-5}alkyl and C_{1-5}alkoxy,

with a compound of Formula V



V

where

R_{10} is hydrogen, hydroxy, C_{1-5}alkoxy, substituted phenyloxy, (where the phenyl substituents are selected from the group consisting of halogen, hydrogen. C_{1-5}alkoxy and C_{1-5}alkyl), substituted phenylC_{1-5}alkyloxy (where the phenyl substituents are selected from the group consisting of halogen, hydrogen. C_{1-5}alkoxy and C_{1-5}alkyl);

in the presence of an acid and a suitable solvent at about reflux, for about 1-6 h to give a compound of Formula I.

The novel compounds of this invention inhibit the in vitro activity of p-38 in the nanomolar range. In addition, the compounds inhibit the in vitro secretion of TNF-α and IL-1β in the nanomolar range. Animal models demonstrate the inhibition of LPS induced TNF-α, as well as the inhibition of rheumatoid arthritis. With this range of activity the compounds of the invention are useful in the treatment of a variety of cytokine related disorders including: rheumatoid arthritis, inflammatory bowel disease, septic shock osteoporosis, osteoarthritis, neuropathic pain, HIV replication, HIV dementia, viral myocarditis, insulin-dependent diabetes, non-insulin dependent diabetes, periodontal disease, restenosis, alopecia areta, T-cell depletion in HIV infection or AIDS, psoriasis, actue pancreatitis, allograft rejection, allergic inflammation in the lung, atherosclerosis, mutiple sclerosis, cachexia, alzheimer's disease, stroke, Crohn's disease, inflammatory bowel disease, ischemia, congestive heart failure, pulmonary fibrosis, hepatitis, glioblastoma, Guillain-Barre Syndrome, and systemic lupus erythematosus.

DETAILED DESCRIPTION OF THE INVENTION

The terms used in describing the invention are commonly used and known to those skilled in the art. However, the terms that could have other meanings are

defined. The term "FCS" represents fetal calf serum, "TCA" represents trichloroacetic acid and the "RPMI" represents the medium from the Roswell Park Memoria Inst. (Sigma cat # R0833). "Independently" means that when there are more than one substituent, the substitutents may be different. The term "alkyl" refers to straight, cyclic and branched-chain alkyl groups and "alkoxy" refers O-alkyl where alkyl is as defined supra. "DME" refers to ethylene glycol dimethyl ether and the term "OTBDMS" refers to [(1,1-dimethylethyl)-dimethylsilyl]oxy. The term "halogen" refers to the group consisting of fluorine chlorine, bromine and iodine radicals and the term "NaHMDS" refers to sodium hexamethyldisilazide. The symbol "Ph" refers to phenyl, and the "aryl" includes mono and fused aromatic rings such as phenyl and naphthyl.

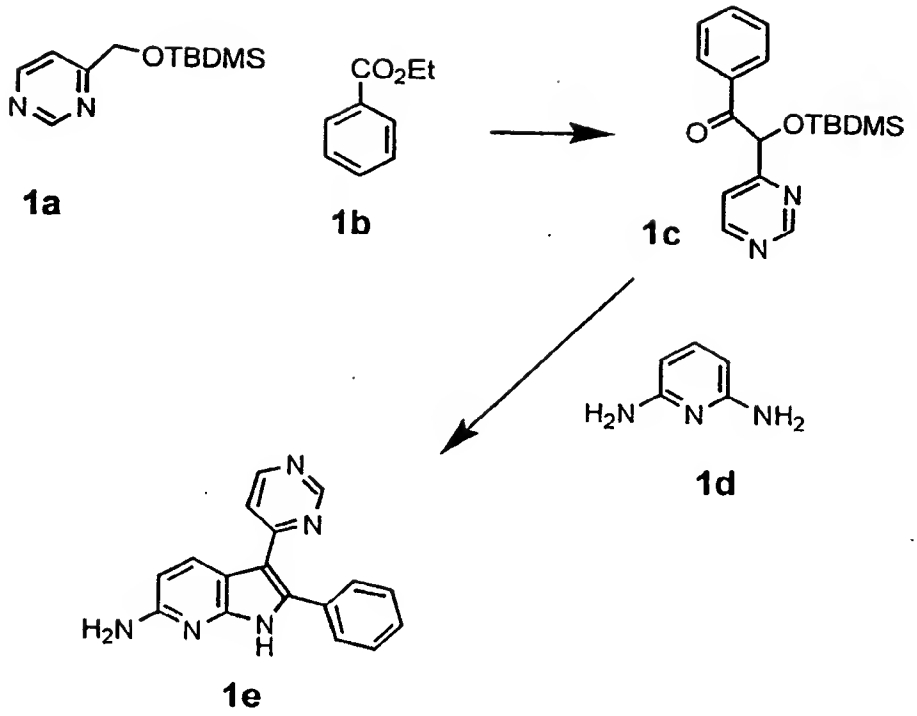
As used in this invention the term "cytokine" refers to the proteins TNF-α and IL-1β. Cytokine related disorders are diseases of humans and other mammals where the overproduction of cytokines causes the symptoms of the disease. The overproduction of the cytokines, TNF-α and IL-1β has been linked to a number of diseases. These cytokine related disorders include but are not limited to rheumatoid arthritis, inflammatory bowel disease, septic shock osteoporosis, osteoarthritis, neuropathic pain, HIV replication, HIV dementia, viral myocarditis, insulin-dependent diabetes, non-insulin dependent diabetes, periodontal disease, restenosis, alopecia areta, T-cell depletion in HIV infection or AIDS, psoriasis, actue pancreatitis, allograft rejection, allergic inflammation in the lung, atherosclerosis, mutiple sclerosis, cachexia, alzheimer's disease, stroke, Crohn's disease, inflammatory bowel disease, ischemia, congestive heart failure, pulmonary fibrosis, hepatitis, glioblastoma, Guillain-Barre Syndrome, and systemic lupus erythematosus. The term "effective dose" refers to an amount of a compound of Formula I which reduces the amount of TNFα and/or IL-1β which may be detected in a mammal suffering from a cytokine mediated disorder. In addition, the term "effective dose" refers to an amount of a compound of Formula I which reduces the symptoms of a cytokine related disorder.

The compounds of the invention may be prepared by the following schemes, where some schemes produce more than one embodiment of the invention. In those cases, the choice of scheme is a matter of discretion which is within the capabilities of those skilled in the art.

Compounds of Formula I may be prepared by Scheme I. An intermediates of type 1a, namely 4-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-pyrimidine, may be stirred with a benzoic ester of type 1b and two equivalents of a suitable hindered base, such as sodium hexamethyldisilazide in a suitable solvent such as THF at room temperature to give the enolate of 1c. Said enolate may be coverted to the corresponding ketone by treatment with a dilute aqueous acid, such as ammonium chloride to give 1c. Examples of other suitable bases include hindered bases such as lithium hexamethyldisilazide, potassium hexamethyldisilazide, and lithium diisopropyl amide. Alternatively compounds of type 1c may be prepared as described by T.F. Gallagher et al. 2,3,5-Triarylimidazole Inhibitors of IL-1 Biosynthesis, 5 *Bioorganic & Medicinal Chemistry Letters,* **1995**,1171-76. Intermediate 1c may be heated with 1d (prepared by the method of D.G. Markees, The Synthesis and Biological Activity of Substituted 2,6-Diaminopyridines, 11 *J. Med Chem* **1968**, 126-29) at reflux over 1-24 h in an inert solvent, such as DME and an acidic agent such as conc. H_2SO_4 to give compounds of type 1e. Example other suitable acidic agents include conc. HCl and polyphosphoric acid. Example of suitable solvents include inert ethers such as THF. Alternatively, one may prepare compounds of Formula I by the methods of R. Herbert, Syntheses and Properties of 1-H Pyrrolo[2,3-b]pyridines , 11 *J. Chem. Soc. C* 1505-14, 1969. However, this method results in only trace amounts of desired products.

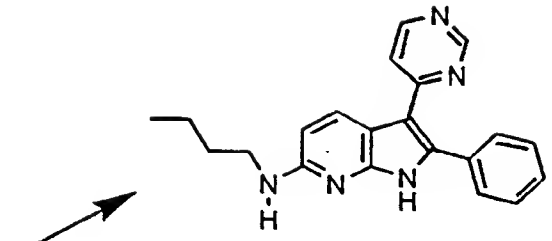
Although the illustrated intermediate produces a compound of Formula I where R_4 is N and R_5 is phenyl, this scheme may be used to produce the compounds of the invention where R_4 is C and R_5 is substituted phenyl by replacing the illustrated intermediates 1a and/or 1b with suitably substituted starting material. In addition, this scheme may be used to produce compounds where R_3 is hydroxy, $C_{1\text{-}5}$alkoxy, phenyloxy, and substituted phenyl$C_{1\text{-}5}$alkyloxy may be prepared via Scheme 1. Replacement of the illustrated 1d with a suitably substituted 2,6-diamino pyridine gives the desired compounds. For example to prepare a compound where R_3 is hydroxy replace the illustrated 1d with 2,6-diaminopyridin-4-ol and carry out the remaining steps of the scheme.

Scheme



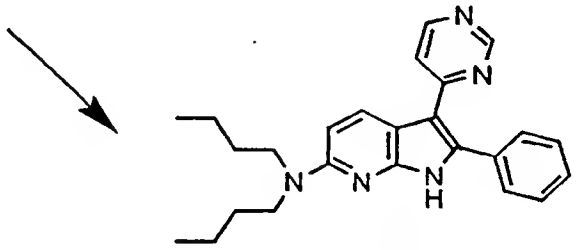
To prepare compounds of Formula I where R_1 is C_{1-5}alkylamino Scheme 2 may be used. Substituted amines may be formed at the unsubstituted amine of 1e by treating 1e with an aldehyde and a reducing agent such as $NaBH_4$ at room temperature for about 10 to 24 h, produces monosubstituted amines of type 2a. The diC_{1-5}alkylamino compounds may be produced using 1e as a starting material and $NaCNBH_3$ as a reducing agent. Aside from the illustrated products and starting material, compounds where R_1 is arylC_{1-3}alkylamino may be produced by this scheme.

Scheme 2



2a

1e

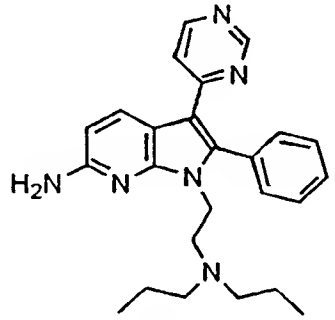


2b

Compounds of Formula I where R_6 is di$C_{1\text{-}5}$alkylamino may be prepared as illustrated in Scheme 3. Treatment of 1e with a base such as NaH in an inert solvent such DMF and an electrophile, such as dipropylaminoethyl chloride at room temperature to 100 °C gives compounds of type 3a.

Scheme 3

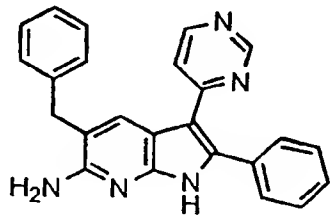
1e



3a

If compounds where R_2 is phenylalkyl, are desired, Scheme 4 may be used to obtain those compounds. Treatment of 1e with an appropriately substituted benzyl alcohol and an aqueous acid give compound 4a.

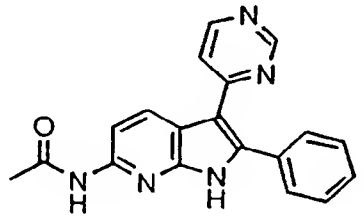
Scheme 4

1e → 

4a

To prepare compounds where R_1 is methylcarbonylamino, Scheme 5 may be used. Treatment of 1e with acetic anhydride and water at room temperature gives compounds of the type 5a.

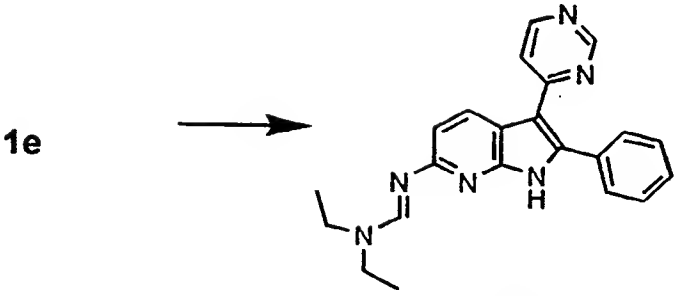
Scheme 5

1e → 

5a

To prepare compounds where R_1 is diethyl-NCH=N-, Scheme 6 may be used as illustrated. Treatment of compound 1e with substituted amino acetals such as diethylformamide dimethyl acetal in an inert solvent such as DMF at about 80 °C gives compounds of type 6a.

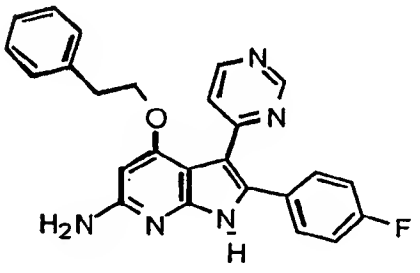
Scheme 6



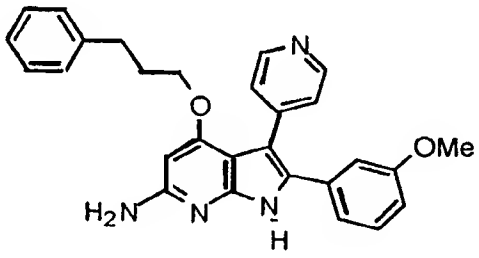
6a

Although the claimed compounds are useful as inhibitors of TNF-α some compounds are more active than others and are either preferred or particularly preferred.

The preferred compounds of the invention include:



and



The particularly preferred "R_1"s are amino and $C_{1\text{-}5}$alkylamino;

The particularly preferred "R_2" is hydrogen.

The particularly preferred "R_3"s are hydrogen, $C_{1\text{-}5}$alkoxy and phenyl$C_{1\text{-}5}$alkoxy.

The particularly preferred "R_4" is -C-.

The particularly preferred "R_5"s are substituted phenyl with one or more substituents selected from fluorine and $C_{1\text{-}3}$alkoxy, where the most preferred R_5 is 4-fluorophenyl;

The particularly preferred "R_6" is hydrogen.

The preferred "R_7 & R_8" are $C_{1\text{-}3}$alkyl.

Compounds of Formula I may be used in pharmaceutical compositions to treat patients (humans and other primates) with disorders related to the overproduction of inflammatory cytokines, particularly TNF-α. The preferred route is oral administration, however compounds may be administered by intravenous infusion or topical administration. Oral doses range from about 0.05 to 100 mg/kg, daily. Some compounds of the invention may be orally dosed in the range of about 0.05 to about 50 mg/kg daily, while others may be dosed at 0.05 to about 20 mg/kg daily. Infusion doses can range from about 1.0 to 1.0×10^4 μg/kg/min of inhibitor, admixed with a pharmaceutical carrier over a period ranging from several minutes to several days. For topical administration compounds of Formula I may be mixed with a pharmaceutical carrier at a concentration of about 0.1 to about 10% of drug to vehicle.

The pharmaceutical compositions can be prepared using conventional pharmaceutical excipients and compounding techniques. Oral dosage forms may be elixers, syrups, capsules tablets and the like. Where the typical solid carrier is an inert substance such as lactose, starch, glucose, methyl cellulose, magnesium sterate, dicalcium phosphate, mannitol and the like; and typical liquid oral excipients include ethanol, glycerol, water and the like. All excipients may be mixed as needed with disintegrants, diluents, granulating agents, lubricants, binders and the like using conventional techniques known to those skilled in the art of preparing dosage forms. Parenteral dosage forms may be prepared using water or another sterile carrier.

Typically the compounds of Formula I are isolated and used as free bases, however the compounds may be isolated and used as their pharmaceutically acceptable salts. Examples of such salts include hydrobromic, hydroiodic, hydrochloric, perchloric, sulfuric, maleic, fumaric, malic, tartatic, citric, benzoic, mandelic, methanesulfonic, hydroethanesulfonic, benzenesulfonic, oxalic, pamoic, 2-naphthalenesulfonic, p-toluenesulfonic, cyclohexanesulfamic and saccharic.

In order to illustrate the invention the following examples are included. These examples do not limit the invention. They are only meant to suggest a method of practicing the invention. Those skilled in the art may find other methods of practicing the invention, which are obvious to them. However those methods are deemed to be within the scope of this invention.

BIOLOGICAL EXAMPLES

The biological activity of the compounds of the invention was demonstrated by in vitro and in vivo assays. As discussed previously, agents

which inhibit the activity of the enzyme p38, inhibit the production of the inflammatory cytokines TNF-α and IL-1β. Compounds of the invention were measured for their ability to inhibit the activity of p38 by the following in vitro assay.

A solution (38 μL) of purified recombinant p38 (where the amount of enzyme was determined empirically considering the linear range of the assay and the acceptable signal to noise ratio; 6xHis-p38 expressed in E.coli), myelin basic protein substrate (also determined empirically), a buffer of pH 7.5 (Hepes:25 mM, $MgCl_2$:10 mM, $MnCl_2$:10 mM) were added to 92 wells of a 96-well round bottom polypropylene plate. The remaining wells were used for control ("CTRL") and background ("BKG"). The CTRL was prepared with the enzyme, substrate buffer and 2% DMSO, and the BKG was prepared with substrate buffer and 2% DMSO. A solution (12 μL) of the test compound in DMSO (compounds were diluted to 125 μM in 10% DMSO/H_2O and assayed at 25 μM where the final DMSO concentration was 2%) was added to the testing wells. The ATP/^{33}P-ATP solution (10 μL: containing 50 μM unlabeled ATP and 1 μCi ^{33}P-ATP) was added to all wells and the completed plates were mixed and incubated at 30 °C for 30 min. Ice-cold 50 % TCA/10 mM sodium phosphate (60 μL) were added to each well and the plates were kept on ice for 15 min. The contents of each well were transferred to the wells of a 96-well filterplate (Millipore, MultiScreen-DP) and the filterplate was placed on a vacuum manifold, fitted with a waste collection tray. The wells were washed five times with 10% TCA/10 mM sodium phosphate (200 μL) under vacuum. MicroScint-20 scintillant was added, the plates were sealed using Topseal-S sheets and counted in a Packard TopCount scintillation counter using a ^{33}P liquid program with color quench correction, where the output is in color quench-corrected cpm. The % inhibition of the test compounds was calculated by the following formula: % inhibition = [1- (sample -BKG)/(CTRL-BKG)] x 100.

Although compounds were initially tested at 10 μM, if warranted the compounds were tested at 4-fold increments above and below that concentration. In addition, IC_{50}s were calculated for some compounds using the Deltagraph 4-parameter curve fitting program.

Aside from the enzyme assay, many of the compounds of the invention were tested in an in vitro whole cell assay using peripheral blood mononuclear cells ("PBMC") which were obtained from human blood as follows. Freshly obtained venous blood was anticoagulated with heparin, diluted with an equal volume of phosphate buffered saline ("PBS") and placed in a sterile tube or other container. Aliquots (30 mL) of this mixture were transferred to centrifuge tubes which were underlaid with Ficoll-Hypaque (15 mL). The prepared tubes were centrifuged at 400 x g without braking for 30 min at room temperature. Approximately 1/2 to 2/3 of the platelet layer above the mononuclear cell band was removed with a pipet. The majority of the mononuclear cell layer was carefully removed using a pipet and these PBMCs were diluted with PBS and spun at 600 x g for 15 min. The resulting PBMCs were washed with another portion of PBS and spun at 400 x g for 10 min at room temperature. The recovered pellets were diluted in low endotoxin RPMI / 1% FCS culture medium and gave a cell concentration of 0.5-2.0 X 10^6 PMBC/ mL. A small volume of the suspension was removed for counting on a hemocytometer and the remaining preparation was centrifuged at 200 x g for 15 min at room temperature. The recovered pelleted PMBC were resuspended in RPMI / 1% FCS to a concentration of 1.67 x 10^6/mL.

To run the assay, the PBMC suspension (180 µL) was transferred to duplicate wells of a 96-well flat-bottom microtiter plate and incubated for 1h at 37 °C. A solution of test compound (10 µL: prepared at 20 x the desired final concentration) was added to each well and the plate was incubated for 1 h at 37 °C. A solution (10 µL) of LPS in RPMI / 1% FCS (200 ng/mL) was added and the wells were incubated overnight at 37 °C. The supernate (100 µL) was removed from each well and diluted with RPMI / 1% FCS (400 µL). The samples were analyzed for TNF-α using a commercial ELISA kit (Genzyme).

The IL-1β activity of select compounds of the invention was determined by the following in vitro assay. Plastic-adherent cells were prepared from PBMC. Briefly, PBMCs were added the wells of a 96-well plate as above, incubated for 1 h at 37 °C, and the adherent cells prepared by gently resuspending the non-adherent cells with a pipetor, removing and discarding them and gently washing the wells 3 times with 200 µL culture medium.

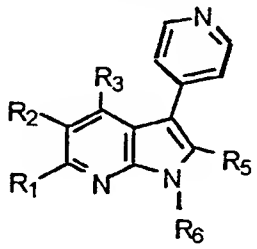
Additional culture medium (180 μL) was added to the wells after the final wash. Compound addition, LPS stimulation, incubation and supernate harvest were as for TNF-α. Supernates were assayed for interleukin-1β using a commercial ELISA (Genzyme). Compound 7 inhibited the production of IL-1β with an IC_{50} of 26 nM.

The ability of the compounds of Formula I to inhibit LPS induced TNF-α production was demonstrated in the following in vivo rodent assays. Mice (BALB / cJ females, Jackson Laboratories) or rats (Lewis males, Charles River) were fasted for 30 min prior to oral dosing with 5-10 mL/kg of test compound at 5-50 mg/kg. Thirty minutes after dosing, the animals were injected intraperitoneally with LPS at 1 mg/kg and returned to their cages for 1 h. Animals were anesthetized by CO_2, exsanguinated by cardiac puncture and whole blood collected (0.1-0.7 mL). The blood was allowed to clot and serum was transferred to a centrifuge tube. This sample was centrifuged, serum was collected, aliquoted and frozen at -80 °C. Samples were tested by commercial ELISAs for TNF-α (Endogen for mouse TNF-α and Biosource for rat TNF-α).

In addition to their in vivo TNF-α activity, a compound of Formula I inhibits polyarthritis in an in vivo rat model as follows. On day 0, male Lewis rats were injected subcutaneously near the base of the tail with 100 ul of a 7.5 mg/ml suspension of heat-killed Mycobacterium butyricum in mineral oil. Groups of rats were dosed orally, once per day, from day 0 through the end of the experiment with HCl as a negative control, or with 20 mg/kg of Cpd. 7. As a positive control for inhibition, one group was dosed with HCl on days 0-9, and then with 20 mg/kg (or 50 mg/kg)of cyclosporine (Cys) from day 10 through the end of the experiment. Under these conditions, the animals' paws in the negative control group begin to swell on days 11-12. The paw volumes of both rear paws were determined on a mercury plesthysmograph on days 8-10, depending on the experiment, and again on days 14, 17, and either 19 or 21. The data were analyzed as the increase in paw volumes compared to the day 8-10 baseline measurements. Compound 7 inhibited the increase in paw volume by 50 %.

Select compounds of the invention are listed in Table A. Compounds were tested for their ability to inhibit p38 and/or TNF-α. Either IC_{50}s are listed or the % inhibition at 10 μm.

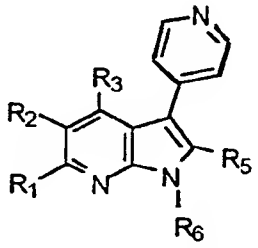
TABLE A



Cpd.	R_1	R_2	R_3	R_5	R_6	p38 IC_{50} μM	TNF-α IC_{50} nM
1	NH_2	H	H	4-F-Ph	H	2.0	33
2	$PhCH_2NH$	H	H	4-F-Ph	H		300
3	$(CH_3)_2NH$	H	H	4-F-Ph	H		650
4	NH_2	H	H	4-F-Ph	$(CH_3)_2N(CH_2)_2$		800
5	$CH_3C(O)NH$	H	H	4-F-Ph	H	73%	100
6	NH_2	$PhCH_2$	H	4-F-Ph	H		55
7	NH_2	H	OCH_3	4-F-Ph	H	77%	6
8	$(CH_3)_2NCH=N$	H	H	4-F-Ph	H		65
10	OH	H	$O(CH_2)_3CH_3$	4-F-Ph	H		15
12	NH_2	H	H	3-I-Ph	H	80%	40
13	NH_2	H	H	3-Cl-Ph	H	91%	9
14	NH_2	H	H	3,4-di-F-Ph	H		30
15	NH_2	H	H	3-Cl, 4-OEt-Ph	H		63
16	NH_2	H	$O(CH_2)_3Ph$	4-F-Ph	H		9
17	NH_2	H	OCH_2Ph	4-F-Ph	H		0.91
18	OCH_3	H	$O(CH_2)_3CH_3$	4-F-Ph	H		6
19	NH_2	H	$O(CH_2)_3CH_3$	4-F-Ph	H		4
20	NH_2	H	OCH_2-3-CH_3OPh	4-F-Ph	H		1.5
21	NH_2	H	OCH_2-4-FPh	4-F-Ph	H	78%	1.7
23	OCH_3	H	H	4-F-Ph	H		200
25	NH_2	Br	H	4-F-Ph	H		103
26	t-butylC(O)NH	H	H	4-F-Ph	H		inactive @ 10 mM
24	OH	H	H	4-F-Ph	H		inactive @ 10 mM

The in vivo test results for select compounds of the invention are listed in Table B. The compounds were tested for their ability to inhibit TNF-α production in mice and/or rats and the data is listed as % inhibition at 25 mg/kg and 10 mg/kg.

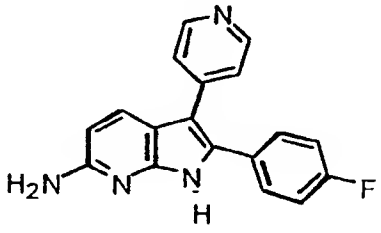
TABLE B



Cpd.	R_1	R_2	R_3	R_5	R_6	%Inhibition TNF-α 25 mg/kg	10 mg/kg
1	NH_2	H	H	4-F-Ph	H	98	73
13	NH_2	H	H	3-Cl-Ph	H	80	22
10	OH	H	$O(CH_2)_3CH_3$	4-F-Ph	H		36
18	OCH_3	H	$O(CH_2)_3CH_3$	4-F-Ph	H	6	
17	NH_2	H	OCH_2Ph	4-F-Ph	H	86	11
19	NH_2	H	$O(CH_2)_3CH_3$	4-F-Ph	H	71	27
21	NH_2	H	OCH_2-4-FPh	4-F-Ph	H	33	11
7	NH_2	H	OCH_3	4-F-Ph	H	98	87

PREPARATIVE EXAMPLES

EXAMPLE 1

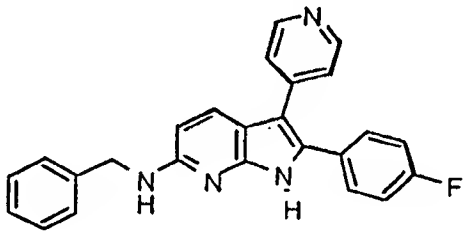


6-Amino-2-(4-fluorophenyl)-3-(4-pyridyl)-1H-pyrrolo [2,3-b] pyridine

Cpd 1

2,6-Diaminopyridine (0.63 g) and 2-[[(1,1-dimethylethyl)dimethylsilyl]--oxy]-1-(4-fluorophenyl)-2-(4-pyridinyl)- ethanone (1.0 g) were dissolved in DME (5 mL) and conc. H_2SO_4 (0.80 mL) was added. The mixture was heated to refluxed for 4 h, cooled to room temperature, poured into water (100 mL) and neutralized with solid K_2CO_3. The aqueous phase was extracted with ethyl acetate (3x50 mL) and the combined organic extracts dried (Na_2SO_4) and concentrated in vacuo. The residue was triturated with ethyl acetate 30 mL to give the title compound as an off white solid (0.44 g). ^1H NMR (300 MHz, DMSO-d6): δ 11.61 (1H, s), 8.48 (2H, d, J=7.6 Hz), 7.63 (1H, d, J=8.6 Hz), 7.42 (2H, m), 7.23 (4H, m), 6.36 (1H, d, J=8.6 Hz), 5.87 (2H, s); Anal. calcd. for $C_{18}H_{13}FN_4$ C 71.04, H 4.31, N 18.41. Found C 70.98, H 4.54, N 18.24.

EXAMPLE 2



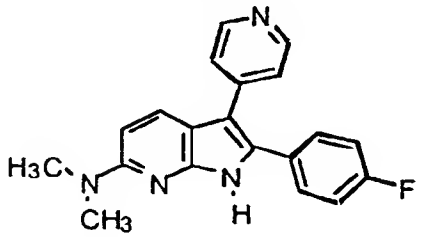
6-N-Benzylamino-2-(4-fluorophenyl)-3-(4-pyridyl)-1H-pyrrolo[2,3-b] pyridine

Cpd. 2

Benzaldehyde (0.035 g) and TsOH (0.005 g) were added to a solution of 2-(4-fluorophenyl), 3-(4-pyridyl)-1H-pyrrolo [2,3-b] pyridin-6-amine (0.10 g) in MeOH (10 mL) followed by 4Å mol. sieves and the mixture was stirred at room temperature for 18 h. $NaBH_4$ (0.025 g) was added and the mixture was stirred another 3 h at room temperature. The solution was neutralized with sat. $NaHCO_3$ solution and extracted with ethyl acetate (3x15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was triturated with ethyl acetate (10 mL) to give the title compound as a white

powder (0.032 g). ^{1}H NMR (300 MHz, DMSO-d6): δ 8.43 (2H, d, J=6.9 Hz), 7.62, 1H, d, J=8.6 Hz), 7.4-7.1 (11H,m), 6.42, 1H, d, J=8.6 Hz), 4.52 (2H, s); MS *m/z* MH^+ 395, 305, 191, 107, 85.

EXAMPLE 3

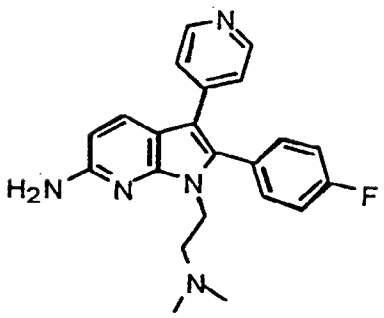


6-N,N-Dimethylamino-2-(4-fluorophenyl)-3-(4-pyridyl)-1H-pyrrolo [2,3-b] pyridine

Cpd. 3

2-(4-Fluorophenyl), 3-(4-pyridyl)-1H-pyrrolo [2,3-b] pyridin-6-amine (0.10 g), paraformaldehyde (0.020g), and sodium cyanoborohydride (0.042g) were dissolved in AcOH (5 mL) at room temperature. The mixture was stirred for 18 h, poured into water, (50 mL) neutralized with solid K_2CO_3 and extracted with ethyl acetate (3x20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to give the title compound as a white solid (0.035 g). ^{1}H NMR (300 MHz, DMSO-d6) δ 8.45 (2H, d, J=6.9 Hz), 7.84 (1H, d, J=8.6 Hz), 7.43 (2H, m), 7.22 (2H, d, J=6.9 Hz), 7.20 (2H, t, J=10.3 Hz), 6.57 (1H, d, J=8.6 Hz), 3.19 (6H, s).

EXAMPLE 4



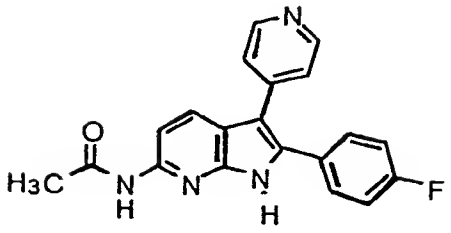
6-Amino-1-(2-dimethylaminoethyl)-2-(4-fluorophenyl)-

3-(4-pyridyl)- pyrrolo [2,3-b] pyridine

Cpd. 4

2-(4-Fluorophenyl), 3-(4-pyridyl)-1H-pyrrolo [2,3-b] pyridin-6-amine (0.175 g) was dissolved in DMF (8 mL). NaH (60%, 0.042 g) was added followed by 2-dimethylaminoethyl chloride hydrochloride (0.067 g), and the mixture was heated at 80 °C for 30 min. After cooling, water (50 mL) was added and the mixture was extracted with ethyl acetate (2x75 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The resulting residue was purified by flash chromotography on silica gel (EtOAc/ MeOH 9/1) to give the title compound as an orange solid (0.022 g). ^1H NMR (300 MHz, DMSO-d6) δ 8.40 (2H, d, J=6.9 Hz), 7.8 (3H, m), 7.39 (1H, d, J=8.6 Hz), 7.28 (1H, t, J=8.2 Hz), 7.10 (2H, d, J=6.9 Hz), 6.43 (1H, d, J=8.6 Hz), 6.05 (2H, s), 4.07 (2H, m), 2.37 (2H, m), 2.00 (6H, s).

EXAMPLE 5



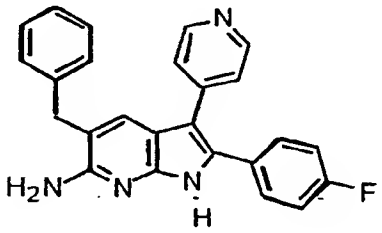
6-Acetamido-2-(4-fluorophenyl)-3-(4-pyridyl)-

1H-pyrrolo [2,3-b] pyridin-6-acetamide

Cpd. 5

Acetic anhydride (1 g) was added to a stirred suspension of 2-(4-fluorophenyl), 3-(4-pyridyl)-1H-pyrrolo [2,3-b] pyridin-6-amine (0.040 g) and water (10 mL) at room temperature. After 2h, the solution was neutralized with solid K_2CO_3 and extracted with ethyl acetate (2x20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to give the title compound as a white solid (0.023 g). ^1H NMR (300 MHz, DMSO-d6) δ 12.12 (1H, s), 10.39 (1H, s), 8.50 (2H, d, J=6.9 Hz), 8.00 (2H, t, J=8.6 Hz), 7.49 (2H, m), 7.28 (4H, m), 3.35 (3H, s).

EXAMPLE 6



6-Amino-5-benzyl-2-(4-fluorophenyl)-3-(4-pyridyl)-

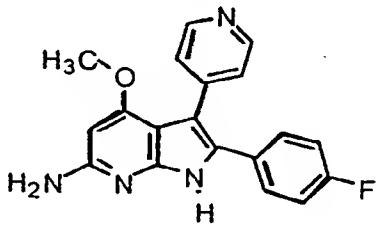
-1H-pyrrolo [2,3-b] pyridine

Cpd 6

A solution of benzyl alcohol (2 mL), compound 1 (0.10 g, 33 mmol) and conc. H_2SO_4 (2 mL) in DME (10 mL) was heated at reflux for 4 h and poured into H_2O. The mixture was neutralized with K_2CO_3,extracted with three portions

of ethyl acetate, and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The mixture was purified by column chromatography on silica gel using ethyl acetate as an eluent to give the title compound as a solid. ^{1}H NMR (300 MHz, DMSO-d6) δ 8.43 (d, 2H, J=6.9 Hz,), 7.62 (1H.J=8.6 Hz), 7.4-7.1 (11H, m), 6.42 (1H, d, J=8.6 Hz), 4.527 (2H, s).

EXAMPLE 7

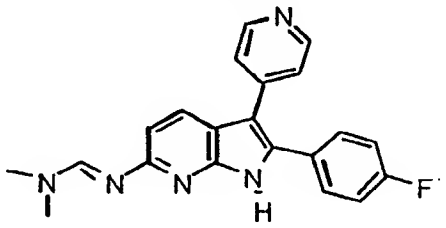


6-Amino-2-(4-fluorophenyl)-4-methoxy-3-(4-pyridyl)-1H-pyrrolo [2,3-b] pyridine

Cpd 7

The title compound was prepared using the method of Example 1, by replacing 2,6-diaminopyridine with 2,6-diamino-4-methoxypyridine, to give the title compound as a solid. ^{1}H NMR (300 MHz, DMSO-d6) δ 11.5 (1H, s), 8.4 (d, 2H, J=7.7 Hz,), 7.3-7.1 (m, 6H), 5.8 (2H, s), 5.8 (2H, bs)3.7 (3H, s).

EXAMPLE 8

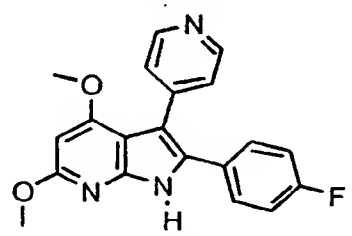


Cpd. 8

Dimethylformamide dimethyl acetal (2 mL) was added to a solution of compound 1 (??) in DMF (5 mL) and the mixture was heated at 80 °C for 3 h. The resulting mixture was cooled to room temperature and triturated with ethyl acetate (10 mL)

to give compound 8 as a solid precipitate. ^{1}H NMR (300 MHz, DMSO-d6) δ 12 (1H, s), 8.8 (1H, d, J=8.6 Hz), 8.5 (3H, m), 7.4 (2H, m), 7.2 (4H, m), 6.7 (1H, d, J=8.6 Hz), 3.1 (3H, s), 3.0 (3H, s).

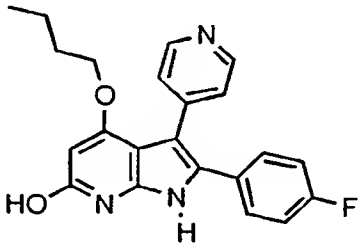
EXAMPLE 9



Cpd. 9

Cpd. 7 (0.72 mmol, 0.24 g) was dissolved in 30 mL MeOH, and conc. HCl was added until the pH was approximately 1. The mixture was cooled to 0 °C and $NaNO_2$ (1.4 mmol, 0.10g) in 1 mL of water was added dropwise. The reaction was allowed to warm to rt over 1h, neutralized with aq. $NaHCO_3$, and extracted with 3x20 mL EtOAc. The organics were dried with Na_2SO_4 and concentrated to 1/4 of the volume. The residue was filtered through a 6 inch silica gel plug using 1:1 hexanes:ethyl acetate to give 55 mg of product. 1H NMR (300 MHz, d_6 DMSO) δ 8.43 (2H, d, J=8.5 Hz), 7.3-7.1 (6H, m), 6.15 (1H, s), 3.91 (3H, s), 3.76 (3H, s).

EXAMPLE 10

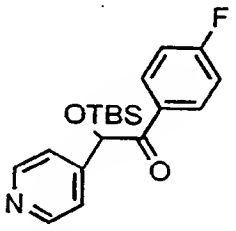


Cpd. 10

2-(4-Fluorophenyl)-4-butoxy-3-(4-pyridinyl)-1H-pyrrolo[2,3-b]pyridin-6-amine) was dissolved in 15 mL of AcOH, cooled to 15 °C and $NaNO_2$ (3.0 mmol, 0.21g) in 3 mL of water was added dropwise. After 15 min, the reaction was heated at 100 C for 1h, cooled and neutralized with aq. K_2CO_3. The resulting solid was collected by filtration and washed with EtOAc to give 0.18 g of product. ^{1}H NMR (300 MHz,

d6 DMSO) δ 8.42 (2H, d, J=8.5 Hz), 7.2 (4H, m), 7.05 (2H, t, J=8.7 Hz), 5.31 (1H,s), 3.81 (2H, t, J=8.1 Hz), 1.43 (2H, m), 1.07 (2H, m), 0.75 (3H, t, J=8.2 Hz).

EXAMPLE 11

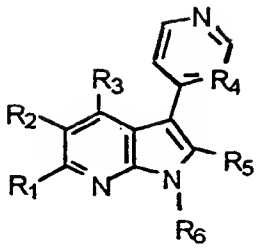


Cpd. 11

4-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-pyridine(0.59 mol, 132.8 g) and 4-fluorobenzoic acid ethyl ester (0.59 mol, 100 g) were dissolved in 1.5 L of THF and a 1.0 M soultion of NaHMDS in THF (1.19 mol, 1.19 L) was added dropwise at rt over 2h. The mixture was stirred with a mechanical stirrer for 18h. The resulting solid was collected by filtration, placed in a beaker containing 1L of sat. aq. NH_4Cl and 1L of Et_2O, and stirred until dissolved. The ether was removed, dried (Na_2SO_4) and concentrated to give pure product cpd. 11 (155g, 76%)

What is claimed is

1. A compound of Formula I



I

wherein:

R_1 is amino, C_{1-5}alkylamino, diC_{1-5}alkylamino, hydroxy, C_{1-5}alkoxy, C_{1-5}alkylcarbonylamino, substituted phenylcarbonylamino where the phenyl substitutents are selected from the group consisting of halogen, hydrogen, C_{1-5}alkly, and C_{1-5}alkoxy, arylC_{1-3}alkylamino or $R_7R_8NCH=N-$

where R_7 and R_8 are independently selected from the group consisting of hydrogen and C_{1-5}alkyl;

R_2 is hydrogen, halogen, phenylC_{1-5}alkyl or substituted phenylalkyl where the phenyl substituents are selected from the group consisting of halogen, hydrogen. C_{1-5}alkoxy and C_{1-5}alkyl;

R_3 is hydrogen, hydroxy, C_{1-5}alkoxy, substituted phenyloxy, (where the phenyl substituents are selected from the group consisting of halogen, hydrogen. C_{1-5}alkoxy and C_{1-5}alkyl), substituted phenylC_{1-5}alkyloxy (where the phenyl substituents are selected from the group consisting of halogen, hydrogen. C_{1-5}alkoxy and C_{1-5}alkyl);

R_4 is -N- or -C-;

R_5 is phenyl or substituted phenyl where the substituents are selected from one to three members of the group consisting of halogen, C_{1-5}alkyl and C_{1-5}alkoxy;

R_6 is hydrogen, C_{1-5}alkyl or diC_{1-5}alkylamino;

and pharmaceutically acceptable salts thereof.

2. The compounds of claim 1 where R_4 is -C-.

3. The compounds of claim 2 where R_5 is substituted phenyl where the phenyl substituent are halogen.

4. The compounds of claim 3 where the phenyl substituent is fluoro.

5. The compounds of claim 3 where R_1 is amino, C_{1-5}alkylamino, or diC_{1-5}alkylamino.

6. The compounds of claim 5 where R_6 is hydrogen and R_2 is hydrogen.

7. The compounds of claim 6 where R_3 is C_{1-5}alkoxy, substituted phenylC_{1-5}alkyloxy where the phenyl substituents are selected from the group consisting of halogen, hydrogen. C_{1-5}alkoxy and C_{1-5}alkyl.

8. A compound and pharmaceutically acceptable salts thereof selected from the group consisting of 6-amino-2-(4-fluorophenyl)-4-methoxy-3-(4-pyridyl)-1H-pyrrolo [2,3-b] pyridine, 6-amino-2-(4-fluorophenyl)-3-(4-pyridyl)-1H-pyrrolo[2,3-b] pyridine, 6-amino-2-(4-fluorophenyl)-4-(n-butyloxy)-3-(4-pyridyl)-1H-pyrrolo[2,3-b] pyridine,6-methoxy-2-(4-fluorophenyl)-4-(n-butyloxy)-3-(4-pyridyl)-1H-pyrrolo[2,3-b] pyridine, 6-amino-2-(4-fluorophenyl)-4-benzyloxy-3-(4-pyridyl)-1H-pyrrolo[2,3-b] pyridine, 6-amino-2-(3-chlorophenyl)-3-(4-pyridyl)-1H-pyrrolo[2,3-b] pyridine, and 6-amino-2-(4-fluorophenyl)-4-(3-methoxybenzyloxy)-3-(4-pyridyl)-1H-pyrrolo[2,3-b] pyridine

9. A compound 6-amino-2-(4-fluorophenyl)-4-methoxy-3-(4-pyridyl)-1H-pyrrolo [2,3-b] pyridine and pharmaceutically acceptable salts thereof.

10. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier or diluent.

11. A pharmaceutical composition comprising a compound according to claim 7 and a pharmaceutically acceptable carrier or diluent.

12. A pharmaceutical composition comprising a compound according to claim 9 and a pharmaceutically acceptable carrier or diluent.

13. A method of treating a cytokine mediated disease comprising administering a compound of claim 1 to a mammal at an effective dose.

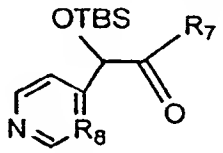
14. A method of treating a cytokine mediated disease comprising administering a composition of claim 9 to a mammal at an effective dose.

15. The method of claim 13 where the compound is administered orally and an effective dose is 0.1-100 mg/kg daily.

16. The method of claim 15 where the dose is 0.1-50 mg/kg daily.

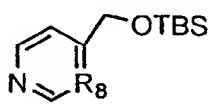
17. A method of treating arthritis comprising administering an effective dose of a compound of Formula I.

18. A method of preparing a compound of Formula II comprising



II

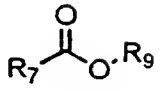
contacting a compound of Formula III



III

where R_8 is -N- or -C-,

with a compound of Formula IV



IV

where

R_7 is phenyl or substituted phenyl where the substituents are selected form one to three members of the group consisting of halogen, C_{1-5}alkyl and C_{1-5}alkoxy,

and

R_9 is C_{1-5}alkyl, phenylC_{1-5}alkyl, or phenyl,

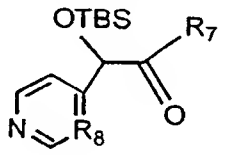
in the presence of suitable base and a suitable solvent at about room temperature to about reflux until the formation of an enolate of a compound of Formula II; and

protonating said enolate with a mild acid to give a compound of Formula II.

19. The method of claim 18 where the suitable base is selected from the group consisting of sodium hexamethyldisilazide, lithium hexamethyldisilazide, potassium hexamethyldisilazide, and lithium diisopropylamine.

20. The method of claim 19 where the suitable solvent is THF and the suitable acid is aqueous ammonium chloride.

21. A method of preparing a compound of Formula I comprising contacting a compound of Formula II



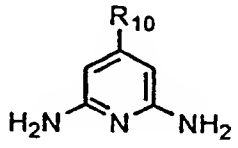
II

where

R_8 is -N- or -C- and

R_7 is phenyl or substituted phenyl where the substituents are selected form one to three members of the group consisting of halogen, C_{1-5}alkyl and C_{1-5}alkoxy,

with a compound of Formula V



V

where

R_{10} is hydrogen, hydroxy, C_{1-5}alkoxy, substituted phenyloxy, (where the phenyl substituents are selected from the group consisting of halogen, hydrogen. C_{1-5}alkoxy and C_{1-5}alkyl), substituted phenylC_{1-5}alkyloxy (where the phenyl substituents are selected from the group consisting of halogen, hydrogen. C_{1-5}alkoxy and C_{1-5}alkyl);

in the presence of an acid and a suitable solvent at about reflux, for about 1-6 h to give a compound of Formula I.

22. The method of claim 21 where the suitable acid is concentrated sulfuric acid and the suitable solvent is ethylene glycol dimethyl ether.

INTERNATIONAL SEARCH REPORT

In. ational Application No
PCT/US 98/07831

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D471/04 A61K31/44 C07F7/18
//(C07D471/04,221:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
A	WO 97 05878 A (MERCK) 20 February 1997 see claims 1,21	1,10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 August 1998	08. 10. 98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	ALFARO FAUS I.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/07831

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 13-17
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 13-17 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(e).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. Claims: 1-17, 21-22
2. Claims: 18-20

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Claims: 1-17, 21-22

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

ernational Application No
PCT/US 98/07831

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9705878 A	20-02-1997	AU 6769196 A	05-03-1997